ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Modified FOLFIRI-Bevacizumab Regimen in the Patients with Metastatic Colorectal Cancer Who Had Progressed After Oxaliplatin-Based Regimen

Oksaliplatin-Temelli Rejim Altında Progresyon Gösteren Metastatik Kolorektal Kanserli Hastalarda Modifiye Folfiri-Bevasizumab Rejimi

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ABSTRACT

Aim: *We aimed to investigate the efficacy and tolerability of modified FOLFIRI-Bevacizumab (mFOLFIRI-B) regime in the second-line treatment of metastatic colorectal cancer (mCRC) patients who received oxaliplatin-based regimen in the first-line treatment.*

Material and Method: *The patients treated with mFOLFIRI-B regimen in second-line therapy who had progressed after oxaliplatin-based chemotherapy were included in this study. The datas of toxicity and efficacy of the regimen were retrospectively evaluated.*

Results: *Total 172 mCRC patients had received mFOLFIRI-B regime in the second-line treatment. 39.5% objective response rate, 9.0 months (7.6 to 10.3) median progression-free survival, 19.0 months (15.1 to 26.2) median overall survival were found. Grade 3/4 toxicity was observed in 33.7%. Grade 3/4 hematologic toxicity was most frequently observed toxicity (31.9%).*

Conclusion: *mFOLFIRI-B is an efficient and safe regimen for the second-line treatment of mCRC patients after the oxaliplatin-based regimen.*

Key words: *metastatic colorectal cancer; second-line chemotherapy; modified FOLFIRI-Bevacizumab*

ÖZET

Amaç: *İlk-sıra tedavide oksaliplatin-temelli rejim alan metastatik kolorektal kanserli (mKRK) hastalarda ikinci-sıra tedavide modifiye FOLFIRI-Bevacizumab (mFOLFIRI-B) rejiminin etkinlik ve tolerabilitesi araştırıldı.*

Materyal ve Metot: *Çalışmaya ilk-sıra tedavide oksaliplatin-temelli rejim alan, ardından progresyon gözlenen ve ikinci-sıra tedavide mFOLFIRI-B rejimi alan mKRK'li hastalar alındı. Toksisite ve etkinlik ile ilgili veriler retrospektif olarak değerlendirildi.*

Bulgular: *Toplam 172 mKRK'li hasta ikinci-sıra tedavide mFOLFIRI-B rejimi almıştı. Hastaların %39,5'inde objektif cevap, 9,0 aylık (7,6 ile 10,3 arası) median progresyonsuz yaşam, 19,0 aylık (15,1 ile 26,2 arası) median tüm yaşam saptandı. Grade 3/4 toksisite %33,7 oranında tespit edildi. Grade 3/4 hematolojik toksisite %31,9 oranında tespit edildi.*

Sonuç: *Sonuç olarak mKRK'li hastalarda oksaliplatin-temelli rejim sonrası ikinci-sıra tedavide mFOLFIRI-B rejimi etkili ve güvenilir bir tedavi rejimidir.*

Anahtar kelimeler: *metastatik kolorektal kanser; ikinci-sıra kemoterapi rejimi; modifiye FOLFIRI-Bevacizumab rejimi*

Introduction

Colorectal cancer is a widespread and fatal disease. While constituting approximately 10% of all cancers, it is the third commonest malignancy in both genders and is the third leading cause of death. It is responsible of 10% of deaths due to cancer[1,2]. The main method of therapy in colorectal cancers is surgical therapy. A part of stage II patients and stage III patients are given adjuvant chemotherapy (CT) following surgical treatment. In stage IV patients, the main treatment approach is systemic CT[2–4]. In rectal cancer, adjuvant or neoadjuvant chemoradiotherapy (CRT) is added in addition to these approaches[5].

Metastatic colorectal cancer (mCRC) constitutes an important part of all colorectal cancers[6]. Survival time increases and symptoms related to the disease are controlled with use of CT[7–9]. Currently, survival time has increased to more then 2 years with new generation CT drugs including oxaliplatin and irinotecan and

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with addition of targeted drugs including bevacizumab and cetuximab[10–14]. In addition, survival rates have been shown to increase further with current efficient CT which renders unresectable metastases resectable and with performed of metastasectomy[15–18].

In treatment of mCRC, combination regimens based on 5-FU are still the main therapeutical options. FOLFOX and FOLFIRI regimens which are constituted by adding oxaliptalin and irinotecan to 5-FU and combination regimes formed by adding bevacizumab and cetuximab are the most frequently used regimens[19–23].

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that selectively binds to vascular endothelial growth factor (VEGF) and inhibits its interaction with its receptor[24]. It has been shown that there is considerable advantage of PFS and OS by usage of 5-FU, leucovorin and irinotecan combination regimen in first line therapy of mCRC[13,25–28]. Nowadays, there is suggestion of combination of bevacizumab with 5-FU, leucovorin plus irinotekan or 5-FU, leucovorin plus oxaliplatin in the first-line therapy of mCRC patients[29].

Generally, in patients with K-ras mutant tumor, combination of bevacizumab with FOLFIRI regimen in first line treatment of mCRC have been accepted as standard therapy. However there are very few reports in the literature about efficieny and toxicities of second-line modified FOLFIRI-Bevacizumab (mFOLFIRI-B) regimen in mCRC patients who had progressed after oxaliplatin-based chemotherapies. It has been shown that bevacizumab containing regimen is an effective therapy in first-line treatment of mCRC patients, therefore it seems to be diffucult to use bevacizumab containing regimens as second-line therapy in any prospective study.

For this reason, evaluating of efficieny and tolerability of mFOLFIRI-B regimen as a second-line therapy is an important topic. Thus the aim of our study is showing retrospectively the efficieny and adverse effects of second-line mFOLFIRI-B regimen in mCRC patients who had progressed after oxaliplatin-based chemotherapies.

Material and Method

Patients

Patients with a diagnosis of mCRC who showed progression under the first-line treatment with oxaliplatin-based regime and received mFOLFIRI-B regime as the second-line treatment between January 2004 and August 2013 were evaluated. The files of the patients were evaluated retrospectively and data about the efficiency of CT, toxicities and survival were obtained.

Patients with stage IV colorectal cancer according to American Joint Committee on Cancer's (AJCC) Cancer Staging 6th edition 2002 TNM grading system who showed progression under the first-line treatment with oxaliplatin-based regime in metastatic period and received mFOLFIRI-B regime as the second-line therapy were included in the study[30].

Treatment

mFOLFIRI-B regime included folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2.400 mg/m^2 46-hour infusion + irinotecan 180 mg/m^2 + bevacizumab 5 mg/kg every 14 days. Modified FOLFOX6 regime included folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2400 mg/m^2 as a 46-hour infusion + oxaliplatin 85 mg/m^2 given once in every 14 days. FOLFOX6 regime included folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2400 mg/m^2 as a 46-hour infusion + oxaliplatin 100 mg/m^2 given once in every 14 days. FOLFOX7 regime included folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2.400 mg/m^2 46-hour infusion + oxaliplatin 130 mg/m^2 every 14 days. XELOX4 regime included capecitabine 2000 mg/m^2 given 2 weeks on 1-week off regimen + oxaliplatin 85 mg/m^2 every three weeks. XELOX7 regime included capecitabine 2000 mg/m^2 given 2 weeks on 1-week off regimen + oxaliplatin 130 mg/m^2 every three weeks.

Response Evaluation

Response was evaluated after every 6 cycles or after three months. Evaluation of response was done according to tumor response assessment criteria of the World Health Organization[31]. Accordingly, disappearance of the tumor completely was considered as complete response (CR), regression of the target lesion with a rate of 50% or more was considered as partial response (PR), regression of the target lesion less than 50% or progression of the target lesion less than 25% was considered as stable disease (SD) and progression of 25% or more in the target lesion or observation of a new lesion was considered as progressive disease (PD). The total of CR and PR was evaluated as objective response rate (ORR).

After 6 cycles CT or after three months, 50% or more reduction in serum carcinoembryonic antigen (CEA) level was considered as tumor marker response. Evaluation of toxicity was done according to National Cancer Institute-Common Toxicity Criteria Version 2.0[32].

The time from the beginning of first cycle day 1 of second-line CT to development of progression or death from any reason was considered as progression-free survival (PFS). The time from the first cycle day 1 of second-line CT to last follow-up or death was considered as overall survival (OS).

Statistical analysis of the data was done using Statistical Package for Social Sciences for Windows (SPSS) Version 15.0 software. Independent group ratios were compared using the chi-square test. Kaplan-Meier method was used for analyses of PFS and OS. Two survival curves were compared using Log-rank Test. The statistical significance was considered as $p < 0.05$.

Results

Patient Features

A total of 172 patients were evaluated. The median age of the all patients was 57 (18–81). 71 (41.3%) patients were female and 101 (58.7%) were male. 98 (56.9%) patients had metastatic colon cancer (Table 1). FOLFOX7 as the first-line regimen was the most common received by patients (Table 2). There was no determined relationship between survival time and first-line CT regimen ($p = 0.568$).

The most commonly observed metastatic organ was the liver (Table 1). 63 (36.6%) of the patients had their primary tumor operated before mFOLFIRI-B regimen was started (Table 2).

Treatment Regimens

The median number of cycles for mFOLFIRI-B regimen was 6 (4–18). After mFOLFIRI-B regime 15 (8.7%) patients received fifth-line CT (Table 2).

Efficiency

ORR was obtained in 68 (39.5%) patients, 11 (6.3%) of these had CR and 57 (33.1%) had PR. Median follow-up time was found to be 42 (7–154) months from the time of metastases was detected. Median follow-up time was 16 (7–69) months from the time of beginning of day 1 of second-line treatment. Median PFS was 9.0 (7.6 to 10.3) months, median OS was 19.0 (15.1 to 26.2) months (Figure 1, 2). Serum level of CEA reduction was observed in 35 (20.3%) patients who had a high level of serum CEA. Primary tumor resection was performed in 12 (6.9%) of the patients and metastasectomy was performed in 14 (8.1%) of the patients. Hepatic metastasectomy was most commonly performed (Table 3).

Toxicity

Grade 3/4 toxicity was observed in 58 (33.7%) patients. Hematologic toxicity was the most commonly observed (31.9%). The most common hematologic toxicity was found to be neutropenia (27.9%). Hypertension and proteinuria which are significant side effects of bevacizumab, was found to be 6.4% and 4.0%, respectively (Table 4).

Discussion

Colorectal cancer is the third leading cancer among all cancers. Approximately half of colorectal cancers are metastatic at the time of diagnosis or become metastatic and need treatment subsequently. Currently, median survival has increased to more than two years due to advances in CT drugs used in recent years. Adding of oxaliplatin or irinotecan to combination of 5FU and leucoverin is mostly accepted CT protocol in treatment of mCRC. The another important point is deciding of second-line CT regimen after progression of following first-line therapy in mCRC. It has been realized that by addition of bevacizumab, a monoclonal antibody the CT response rate has increased. Therefore bevacizumab mostly has been used in first-line CT which is critical point. But especially in patients who had progressed after oxaliplatin-based regimen, the rate of efficieny and tolerability of addition of bevacizumab to second-line CT is exactly not known. This situation same in patients with K-ras mutant tumor. Thus the data in adding bevacizumab to mFOLFIRI will become important. From the point of this reason, we aim to evalutate datas of mFOLFIRI-B as a second line therapy of 172 patients who had progressed after oxaliplatin-based CT.

Combination of 5-FU/leucovorin is the first important regimen that had been used in mCRC patients and by this regimen 5 years OS is below the 1%[33]. Nowadays by applying modern CT regimens and metastasectomies, rate of 5 years OS is nearly equal to 30%[34].

Table 1. *General characteristics of the patients*

Characteristic		n (%)
Gender		
Female		71 (41.3)
Male		101 (58.7)
Primary tumor localization		
Colon		98 (56.9)
	Right	26 (15.1)
	Middle	28 (16.2)
	Left	44 (25.6)
Rectum		74 (43.1)
	Upper	22 (12.8)
	Middle	23 (13.4)
	Lower	29 (16.9)
Histopathology		
Adenocarcinoma		148 (86.1)
Other		24 (13.9)
Metastatic organ		
Liver		114 (66.2)
Findings indicating intraabdominal tumor invasion		54 (31.3)
Lung		43 (25.0)
Bone		19 (11.0)
Supraclavicular lymph node involvement		5 (2.9)
Spleen		3 (1.7)
Ovary		2 (1.1)
Metastasis in two organs		41 (23.8)
Metastasis in more than two organs		27 (15.6)
Serum CEA		
5 ng/mL and higher		145 (84.4)
Lower than 5 ng/mL		27 (15.6)

CEA, Carcinoembryonic antigen.

Table 2. *Other characteristics of the patients*

	n (%)
History of primary tumor operation	63 (36.6)
History of adjuvant CT	34 (19.7)
History of neoadjuvant CRT	25 (14.5)
History of adjuvant CRT	6 (3.4)
In first-line CT regimes	
Modified FOLFOX6	19 (11.1)
FOLFOX6	5 (2.9)
FOLFOX7	117 (68.0)
XELOX4	9 (5.2)
XELOX7	22 (12.8)
In second-line CT regime	172 (100.0)
Modified FOLFIRI-Bevasizumab	172 (100.0)
Third-line CT received patients	75 (43.6)
Fourth-line CT received patients	34 (19.7)
Fifth-line CT received patients	15 (8.7)

CT, Chemotherapy; CRT, Chemoradiotherapy.

Table 3. *Efficacy provided by the treatment administered*

	Month (95% CI)	%	n (%)
Median PFS	9.0 (7.6–10.3)		
Median OS	19.0 (15.1–26.2)		
1 year OS		69.0	
3 years OS		25.0	
5 years OS		13.5	
Complete response			11 (6.4)
Partial response			57 (33.1)
All response rates			68 (39.5)
Stable disease			42 (24.4)
Progressive disease			62 (36.0)
Patients who had undergone primary tumor resection			12 (6.9)
R0 resection			10 (5.8)
R1 resection			2 (1.1)
Patients who had undergone metastasectomy			14 (8.1)
R0 resection			11 (6.4)
R1 resection			3 (1.7)
Liver metastasectomy			10 (5.8)
Peritonectomy			5 (2.9)
Lung metastasectomy			5 (2.9)
Splenectomy			1 (0.5)
Patients whose serum CEA levels decreased			38 (22.0)
Patients whose serum CEA level decreased below 5 ng/mL			12 (6.9)

PFS, Progression-free survival; DFS, Disease-free survival; OS, Overall survival; CEA, Carcinoembrionic antigen.

Table 4. *Side effects caused by treatment*

Characteristic	Grade ½ side effects n (%)	Grade ¾ side effects n (%)	n (%)
All	113 (65.6)	58 (33.7)	
All hematological side effects	98 (56.9)	55 (31.9)	
Neutropenia	65 (37.7)	48 (27.9)	
Anemia	52 (30.2)	23 (13.3)	
Thrombocytopenia	41 (23.8)	19 (11.0)	
Nausea/vomiting	44 (25.6)	32 (18.6)	
Diarrhea	29 (16.9)	18 (10.4)	
Oral mucositis	32 (18.6)	14 (8.1)	
Hand foot syndrome	17 (9.8)	8 (4.6)	
Allergic reaction	8 (4.6)	2 (1.1)	
Neurotoxicity	4 (2.3)	2 (1.1)	
Hypertension			11 (6.4)
Proteinuria			7 (4.0)
Skin eruption			7 (3.9)
Gastrointestinal bleeding			4 (2.3)
Neutropenic fever			3 (1.7)
Deep vein thrombosis			2 (1.1)

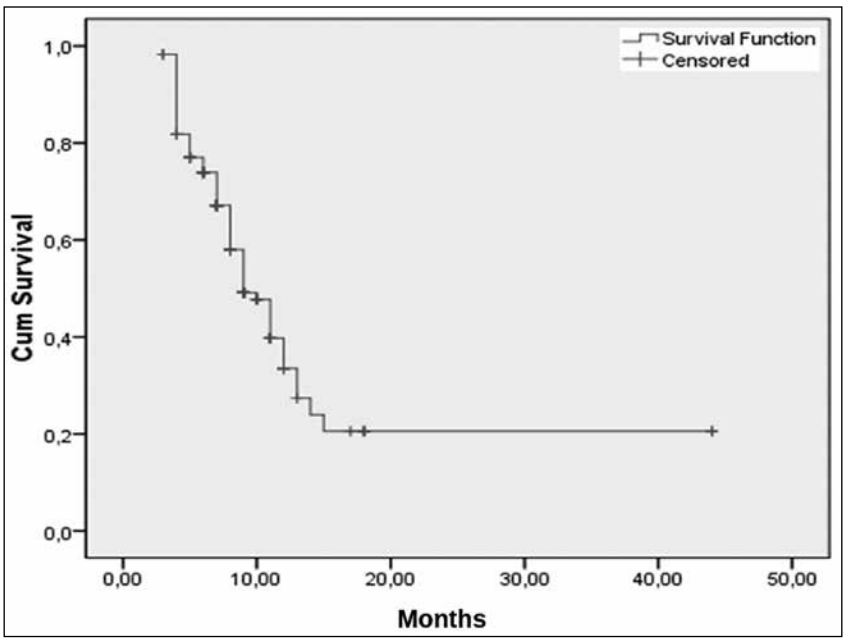

Figure 1. *Progression-free survival (median 9.0 months).*

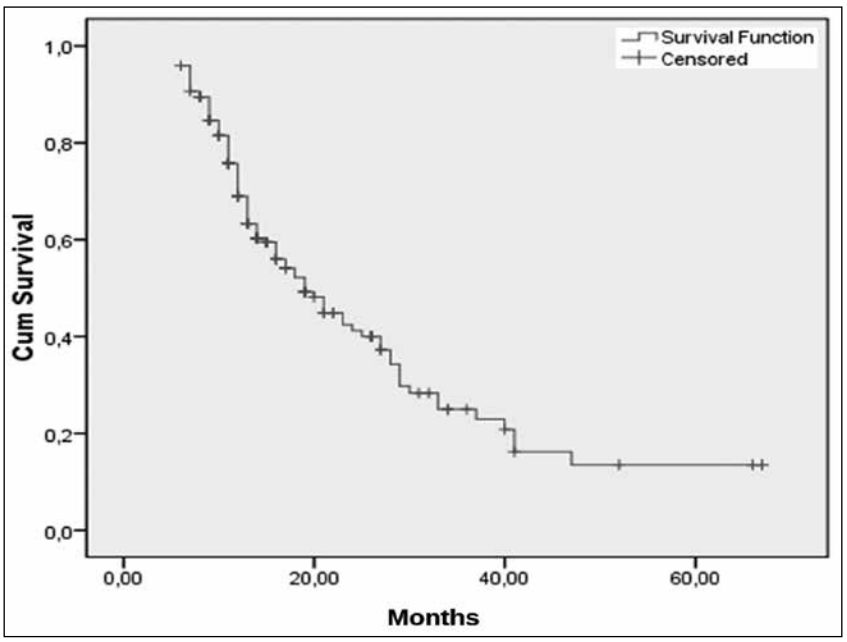

Figure 2. *Overall survival (median 19.0 months).*

Among the new chemotherapeutic agents, bevacizumab, a monoclonal antibody, is the first the drug that has been added to CT. By usage of bevacizumab in first-line therapy, survival has been getting quite longer. In a study that had used the combination of bevacizumab and irinotecan, bolus 5-FU-leucovorin (IFL regimen) in first-line therapy, by addition of bevacizumab to CT regimen, an important survival advantage has been achieved[13]. Infusional 5-FU is more effective in mCRC. By the way it has been shown that FOLFIRI regimen is much more useful comparing to IFL regimen and another study showed that the addition of bevacizumab to FOLFIRI regimen had better PFS and OS results[28,35].

There are some studies that had used a bevacizumab containing regimen as second or third line therapy in mCRC patients that progressed after first-line therapy. Regarding this, there is an important study that used oxaliplatin, 5-FU, leucoverin and bevacizumab (FOLFOX4-B) as a second-line therapy after progression of patients with mCRC. By this treatment option there was a advantage of OS[36]. As a result of showing effiency of bevacizumab in combination with oxaliplatin in second line therapy, a multicenter study using bevacizumab in combination with FOLFIRI regimen in second line treatment was performed. By this study, advantage of 8.3 months median PFS and 21.6 months median OS were achieved[37].

Although bevacizumab has survival advantage in combination with first-line CT, it has been shown that after progression of disease there is still survival advantage of using bevacizumab in combination with second-line treatment[38].

There is concensus about usage of bevacizumab in first-line therapy. It has not still being clearly defined that there is survival advantage of adding bevacizumab to mFOLFIRI regimen as a second-line therapy in patients who had previously used different CT regimens. Since mCRC patients are now huge populations, collecting data about mFOLFIRI-B as second-line therapy is becoming very important.

However, in our study, grade 3/4 toxicity was observed in 33.7% of the patients. Grade 3/4 neutropenia was observed 27.9% of the patients. Side effects of bevacizumab, hypertension and proteinuria was found to be 6.4% and 4.0%, respectively. This findings suggest that mFOLFIRI-B may be tolerated regimen for side effects.

Since this study was a retrospective study, it has disadvantages related to retrospective studies. However, regarding a subject like treatment of mCRC which concerns a large number of patients, we thought that it would be beneficial to present mFOLFIRI-B regime in the second-line treatment which showed progression under the oxaliplatin-based regime in the first-line treatment of mCRC patients to the literature, though we used retrospective data.

Consequently, we can state that mFOLFIRI-B regime provides a significant survival advantage in second-line treatment of mCRC patients in whom progression was detected after the oxaliplatin-based regime in the first-line treatment. It provides reduction in the volume and number of the metastatic tumor, makes it easy to metastasectomy, increases PFS and OS and has easly managable side effects. We think that there is a need to make prospective studies for clerance of this topic.

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